Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendments, claims 27-56 and 102-219 are pending in the application. Claims 57-101 have been canceled without prejudice or disclaimer. Applicants retain the right to pursue the subject matter of the canceled claims in one or more continuing applications. Claims 122-219 have been newly added. The new claims correspond to the subject matter of canceled claims 57-101 and do not include new matter. Accordingly, Applicants respectfully request entry of the amendments.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Pending Claims 120 and 121

On June 21, 2001, a Continued Prosecution Application (CPA) and Preliminary Amendment were filed in the captioned application. A copy of the complete filing was re-submitted with the Petition to Withdraw Holding of Abandonment on October 9, 2001. In the Preliminary Amendment, Applicants sought the addition of new claims 120 and 121. However, in the instant Office Action, the Examiner has indicated that only claims 27-119 are pending in the application. (Paper No. 18, page 1.) Applicants respectfully request that the Examiner correct and/or provide an explanation for the discrepancy.

The Prematureness of the Final Office Action

Applicants believe that the issuance of the final Office Action (Paper No. 18) is premature and request withdrawal of its finality. The Examiner has stated that:

> All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds of art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114.

(Paper No. 18, pages 5-6.)

Contrary to the Examiner's statement, Applicants have not filed a submission under 37 C.F.R. § 1.114, i.e., a Request for Continued Examination. Rather, on June 21, 2001 a Continued Prosecution Application (CPA) under 37 C.F.R. § 1.53(d) was filed in the instant application. In addition to the CPA, a Preliminary Amendment was filed on June 21, 2001 in which Applicants added new claims 120-121. Accordingly, all claims were not "drawn to the same invention claimed in the application prior to the entry of the submission under 37 C.F.R. § 1.114." Thus, Applicants believe that the finality of the instant Office Action is improper and respectfully request that it be withdrawn.

Objection to the Claims

The Examiner has indicated that the objection to claims 57, 62-70, 73-81 and 94-100 has been maintained because the claims recite an allegedly improper Markush group. (Paper No. 18, page 2.) For the reasons already on record, Applicants respectfully disagree with the Examiner. However, in an effort to advance prosecution, claims 57, 62-70, 73-81 and 94-

100 have been canceled in favor of new claims 122-219. The new claims do not utilize the Markush format. Accordingly, the Examiner's objection is rendered moot.

Claim Rejections Under 35 U.S.C. § 101

The Examiner has rejected claims 27-119 under 35 U.S.C. § 101 because allegedly, the claims are "drawn to an invention with no apparent disclosed specific and substantial credible utility." (Paper No. 18, page 2.) For the following reasons, Applicants respectfully disagree and traverse the Examiner's rejection.

Initially, the Examiner is reminded that Applicants need only provide one credible assertion of specific and substantial utility for the claimed invention to satisfy the utility requirement. (Federal Register, Vol. 66, No. 4, Friday, January 5, 2001, 1098.) "When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. § 101 is clearly shown." *Raytheon v. Roper*, 724 F.2d 951, 958 (Fed. Cir. 1983). According to the M.P.E.P., a specific utility is specific to the subject matter claimed, in contrast to a utility that would be applicable to the broad class of the invention. A substantial utility defines a "real world" use. (M.P.E.P. § 2107.01(I).) For example, a therapeutic method of treating a known or newly discovered disease has a substantial utility and defines a "real world" use. (*Id.*)

Contrary to the Examiner's contentions, the claimed invention has at least one specific, substantial and credible asserted utility. The specification teaches that the polypeptides encoded by the claimed polynucleotidess can, among other things, be used to generate agonists of DR3-V1 and DR3. *Such a utility does not require identification of a ligand.* An agonist is defined as an agent, e.g. an antibody, which is capable of increasing

DR3-V1 or DR3 mediated signaling. (Specification, page 6, lines 1-5; page 39, lines 3-11.) Preferably, DR3-V1 or DR3 mediated signaling is increased to treat a disease wherein decreased apoptosis is exhibited. (*Id.* at page 39, lines 7-11.) According to the specification, a specific disease where decreased apoptosis is exhibited is autoimmune disease. (Page 38, lines 18-21.) Moreover, the specification states that:

> Apoptosis-programmed cell death-is [sic] a physiological mechanism involved in the deletion of peripheral T lymphocytes of the immune system, and its dysregulation can lead to a number of pathogenic processes.

(Page 38, lines 13-16.) The specification also teaches that DR3 can play a role in lymphocyte homeostasis. (Page 63, lines 18-19.)

The use of the polypeptides encoded by the claimed polynucleotides to generate DR3-V1 and DR3-specific agonists, e.g., agonistic antibodies, is a specific utility not applicable to the broad class of the invention—i.e., not all polypeptides can be used to generate DR3-V1 and DR3-specific agonists. (*See* M.P.E.P. § 2107.01 (I).) Further, the use of the polypeptides encoded by the claimed polynucleotides to generate specific agonists is a substantial utility, as the treatment and prevention of autoimmune diseases, and diseases associated with the T lymphocyte disregulation and lymphocyte homeostasis constitute "real world" utilities. (*See* M.P.E.P. § 2107.01 (I).) Moreover, further research, such as the identification of a native ligand, is not required to actually use the polypeptides encoded by the claimed polynucleotides in the treatment and prevention of autoimmune diseases. All that is required is the routine generation of agonistic antibodies. Accordingly, the polypeptides encoded by the claimed polynucleotides have a specific and substantial utility.

Based, in part, on the homology of the polypeptides encoded by the claimed polynucleotides to TNF R1 and Fas (Figure 3), the tissue distribution of DR3 gene

expression (Example 4), the presence of the death domain within DR3, and the confirmed biological activity of DR3 (Example 6), one of ordinary skill in the art would find the asserted utilities credible and "more likely than not" true.

However, in case the Examiner has doubts about the credibility of Applicants' assertions, Applicants submit herewith two publications, Tartaglia & Goeddel, *J. Biol. Chem.* 267: 4304-4307 (1992) (Exhibit A) and Wang *et al.*, *Mol. Cell. Biol.* 21: 3451-3461 (2001) (Exhibit B), and a poster produced by the assignee and a collaborator entitled "TRM-1, A Human TRAIL-R1 Agonistic Monoclonal Antibody, Displays In Vitro and In Vivo Anti-tumor Activity" by Salcedo *et al.* (attached as Exhibit C).[1] The publications and poster provide support that the following assertions are credible:

(A) Agonistic antibodies against DR3-V1 and DR3 can be utilized to trigger DR3 and/or DR3-V1 meditated signaling; and

(B) Agonistic antibodies against DR3-V1 and DR3 can be utilized to treat and/or prevent specific disorders, e.g., autoimmune diseases and diseases associated with lymphocyte homeostasis and T-cell dysregulation.

Tartaglia & Goeddel state that "[b]oth polyclonal and monoclonal antibodies directed against human TNF-R1 have been shown to behave as receptor agonists and elicit several TNF activities such as cytotoxicity, fibroblast proliferation, resistance to chlamydiae and

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[1] Throughout this response, Applicants provide the Examiner with both pre-filing date and post-filing date references for no other purpose than to substantiate any doubts about utility. In *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), the Federal Circuit expressly recognized the use of post-filing date declarations and references to substantiate any doubts as to an asserted utility of an invention so long as the reference "pertains to the accuracy of a statement already in the specification." (*Id.* at 1567 n.19.) Thus, Applicants submit that the use of post-filing date references and the data provided therein to support assertions of utility with respect to the instant invention is proper.

synthesis of prostoglandin E_2." (Tartaglia & Goeddel at 4304, column 2 (citations removed).) In their own experiments, Tartaglia & Goeddel show that the 55-kDa TNF receptor, stably expressed in mouse L929 cells, was activated specifically by agonist antibodies and initiated the signal for cellular cytotoxicity. (*Id.* at column 1.)

Salcedo *et al.*, also studying agonistic antibodies of TNF receptors, found that TRM-1, a human agonistic antibody specific for TRAIL R1, induced apoptosis in human cancer cell lines *in vitro* and reduced tumor growth in human colon and uterine xenograft models in nude mice. (*See* Conclusions, columns 5-6.) In addition, TRM-2, a human agonistic antibody specific for TRAIL R2, was found to be effective in reducing or preventing tumor growth in human colon xenograft models in nude mice. (*Id.*) As the polypeptides encoded by the claimed polynucleotides are also members of the apoptosis-inducing subfamily of TNF family of receptors studied by Tartaglia & Goeddel and Salcedo *et al.*, Applicants submit that the teachings of Tartaglia & Goeddel and Salcedo *et al.* support the assertion that agonistic antibodies of the polypeptides encoded by the claimed polynucleotides can be used to trigger DR3-V1 and/or DR3 activity.

The Examiner's attention is further directed to the teachings of Wang *et al.*, which further provides support that agonistic antibodies of DR3-V1 and DR3 can be used to treat and/or prevent specific diseases and disorders. Specifically, Wang *et al.* studied the *in vivo* role of DR3 by generating mice congenitally deficient in the expression of the DR3 gene. (Wang *et al.*, page 3451, abstract.) They show that negative selection and anti-CD3 -induced apoptosis are significantly impaired in DR3-null mice. (*Id.*) Wang *et al.* indicate that, in contrast, both superantigen-induced negative selection and positive selection are normal. (*Id.*) Further, they show that the pre-T-cell mediated checkpoint, which is

dependent on TNFR signaling, is also unaffected in DR3-deficient mice. (*Id.*) Wang *et al.* conclude that:

> [t]hese data reveal a nonredundant in vivo role for this TNF receptor family member in the removal of self-reactive T cells in the thymus.

(*Id.*) Thus, Wang *et al.* provide support that agonists of the polypeptides encoded by the claimed polynucleotides can be used in the treatment and/or prevention of, for example, autoimmune diseases, diseases associated with lymphocyte homeostasis and T-cell dysregulation, as asserted in the specification and discussed above.

Aside from generating agonistic antibodies, one of ordinary skill in the art would find it reasonable to believe that soluble forms of the polypeptides encoded by the claimed polynucleotides are also useful for therapeutic purposes. For example, the specification states that:

> [S]oluble forms of the receptor, which may be naturally occurring or synthetic, antagonize DR3-V1 or DR3 mediated signaling by competing with the cell surface DR3-V1 or DR3 for binding to TNF-family ligands. Thus, soluble forms of the receptor that include the ligand binding domain are novel cytokines capable of inhibiting apotosis induced by TNF-family ligands. These are preferably expressed as dimers or trimers, since these have been shown to be superior to monomeric forms of soluble receptor as antagonists.

(Page 43, lines 12-18.) Thus, contrary to the Examiner's comments, Applicants argue that one utility of the instant invention lies in the effect that the soluble receptor will have on endogenous DR3-V1 and DR3 receptors or available ligands of DR3-V1 and DR3. In this use, administration of the isolated polypeptides of the claimed invention can regulate apoptosis by interacting with endogenous receptor, or binding free ligand, thereby preventing the ligand from binding endogenous receptors and triggering apoptosis.

In support of this utility, Applicants direct the Examiner to Migone *et al.*, *Immunity* 16: 479-492 (2002) (Exhibit D). Migone *et al.* not only identify the ligand of DR3 as TL1A, they also indicate that TR6, a TNFR family member lacking a cytoplasmic domain, acts as a "decoy" receptor and may act as an inhibitor of apoptosis by competing with the signal tranducing receptor for the ligand. Similarly, providing excess soluble receptor of the polypeptides encoded by the claimed polynucleotides could conceivably function in the same way as the known "decoy" receptor (TR6) by competing for TL1A. Accordingly, polypeptides encoded by the polynucleotides of the invention can act as "decoy" receptors and therefore have uses in the regulation of apoptosis and suppression of proinflammatory responses to TL1A stimulation. To that end, the specification teaches the relevant structural regions (extracellular, intracellular, and transmembrane domains) of the polypeptides encoded by the claimed polynucleotides at, for example, page 14, lines 12-19.

Applicants note that there are commercially available examples of soluble TNF receptors being used as a pharmaceutical in manner similar to the decoy receptor utility described above. Enbrel™ is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human TNF receptor. (*See* Exhibit E.) Enbrel™ works by binding specifically to TNF and blocking its interaction with cell surface receptors, rendering TNF biologically inactive. One of ordinary skill in the art would find it credible that the claimed invention could be used in a similar fashion.

Compliance with 35 U.S.C. § 101 requires only demonstration that a single utility of the claimed invention is specific, substantial and credible. Applicants note that in addition to the therapeutic utilities described in detail above, the polynucleotides of the claimed invention have other specific, substantial and credible uses in the diagnosis of

autoimmune diseases. In light of the teachings of Wang *et al.* (Exhibit B), demonstrating a non-redundant role played by DR3 in the elimination of autoreactive T-lymphocytes, the skilled artisan would expect that detection of DR3 expression can aid in the diagnosis of autoimmune diseases as taught in the specification as originally filed.

In view of the above, it is clear that at least one asserted utility of the claimed polypeptide is specific, substantial and credible. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has maintained his rejection of claims 27-119 under 35 U.S.C. § 112, first paragraph. (Paper No. 18, page 5.) The Examiner contends that since the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well-established utility, for the reasons above with regards to the rejection under 35 U.S.C. § 101, one skilled in the art would not know how to use the claimed invention.

In view of the above, the claimed invention has a patentable utility under 35 U.S.C. § 101. The Examiner "should not impose a 35 U.S.C. § 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. § 101 rejection is proper." (M.P.E.P. § 2107(IV) at 2100-28.) Therefore, since the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the rejection of claims under 35 U.S.C. § 112, first paragraph, based on lack of utility of the claimed invention, should be withdrawn.

Claim Rejections Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 27-119 under 35 U.S.C. § 102(b) as allegedly being anticipated by Kitson *et al.*, *Nature* 384:372-375 (1996). (Paper No. 18, page 5.) The Examiner contends that the cited reference is prior art because the priority applications of the present case are unavailable under 35 U.S.C. § 120. The Examiners' rationale is that because the present application doesn't meet the requirements of 35 U.S.C. § 112, first paragraph, the prior applications also do not meet this requirement. Applicants respectfully traverse this rejection.

As discussed above, Applicants believe that the requirements of 35 U.S.C. § 112, first paragraph, have been satisfied for the present application. The requirements of 35 U.S.C. § 112, first paragraph, have also been satisfied for the earlier priority applications. Accordingly, Applicants submit that Kitson *et al.* is not available as prior art. Reconsideration and withdrawal of the rejection are respectfully requested.

Request for an Interview

Applicants believe that the above discussion properly traverses, accommodates, or renders moot all of the stated grounds of objection and rejection. However, in the event that the Examiner disagrees and maintains the rejections, Applicants respectfully request that an interview be granted with the undersigned prior to issuance of another Office Action or Advisory Action.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

The application has been amended as follows:

In the Claims:

Claims 57-101 have been canceled.

Claims 122-219 have been newly added.